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09/08/2003

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EXAMINER

HUI, SAN MING R

ART UNIT

PAPER NUMBER

1617

DATE MAILED: 09/08/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/982,554

Applicant(s)

ZOHOUNGBOGBO, MATHIAS C.

Examiner

San-ming Hui

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 19 June 2003.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 26-40 is/are pending in the application.
- 4a) Of the above claim(s) 40 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 26-39 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All   b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

Applicant's amendments filed June 19, 2003 have been entered.

The addition of claim 40 is acknowledged.

Claims 26-40 are pending.

Newly submitted claim 40 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The method of reducing fibrogen is unrelated to and independent from the method of treating the side-effect of ketogenic diet.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 40 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

The outstanding rejections under 35 USC 112, second paragraph of claims 26-31, 33-38 are withdrawn in view of the amendments filed June 19, 2003.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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The expression of "any tiroxine analogs" in claim 32 renders the claims indefinite as to what compounds are encompassed by the claims. It is not clear what compounds are considered as tiroxine analogs and what are not. Therefore, one of ordinary skill in the art would not ascertain the metes and bounds of the claims.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 26, 29, 30, 33, and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marquie et al. (Life Sciences, 1998; 63(1):65-76), Pentikainen et al. (Annals of Medicine, 1990 ;22 :307-312), and Poupon et al. (Hepatology, 1993; 17(4): 577-582) in view of Spasmo-canalase® Bitab® package insert (July 1989).

Marquie et al. teaches benfluorex as useful in treating hypercholesterolemia (See abstract, also page 74, whole page).

Pentikain et al. teaches the cholesterol lowering affect of metformin (See the abstract, also page 309, Table 2).

Poupon et al. teaches ursodesoxycholic acid as useful in lowering hypercholesterolemia (See particularly the abstract).

The references do not expressly teach the method of treating the side effects of a ketogenic diet with the combination of benfluorex, metformin and ursodesoxycholic acid. The references do not expressly teach the herein claimed amount ratio employed. The references do not expressly teach the employment of pancreatin and sodium dehydrocholate with benfluorex and metformin.

Spasmo-canulase<sup>®</sup> Bitab<sup>®</sup> package insert teaches Spasmo-canulase<sup>®</sup> Bitab<sup>®</sup> , which contains pancreatin and sodium dehydrocholate, is useful in treating abdominal camps associated with flatulence.

One of ordinary skill in the art would have been motivated to treat side effects of a ketogenic diet (hypercholesterolemia being one of the side effects of ketogenic diet) with the combination of benfluorex, metformin and ursodesoxycholic acid. Combining and employing two or more agents which are known to be useful to lowering hypercholesterolemia individually into a single method useful for the very same purpose (treating hypercholesterolemia) is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069. One of ordinary skill in the art would have been motivated to incorporate pancreatin and sodium dehydrocholate in the treatment method herein because Spasmo-canulase<sup>®</sup> Bitab<sup>®</sup> , which contains pancreatin and sodium dehydrocholate, is known for relieving abdominal cramps associated with flatulence. Since flatulence and

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abdominal cramps are the common side effects of metformin, employing Spasmo-canulase® Bitab® would be reasonably expected to be effective in relieving the side effects of metformin and be useful in the herein claimed method, which utilize metformin. Furthermore, the optimization of result effect parameters (i.e., dosage range, dosing regimens) is obvious as being within the skill of the artisan.

Claims 27, 28, 31-32, 34-35, and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marquie et al., Pentikainen et al., Poupon et al., and Spasmo-canulase® Bitab® package insert as applied to claims 26, 29, 30, 33, and 36-37 above, and further in view of Hydrocotyle (A Modern Herbal Home Page, 1995), Kang et al. (Archives of Physiology and Biochemistry, 1997;105(6):603-607), Pondimin monograph (PDR, 1996, page 2066-2067), and Keown et al. (WO 95/11034).

Marquie et al., Pentikainen et al., Poupon et al., and Spasmo-canulase® Bitab® package insert suggest the method of treating side effects of ketogenic diet by employing the herein claimed agents.

The references do not expressly teach the ketogenic diet side effects treating method employing also centella asiatica triterpene, selenium, yohimbine, phendimetrazine, and fenfluramine in the herein claimed amount.

Hydrocotyle teaches that centella asiatica is known to be a mild stimulant (See the Medicinal Action and Uses Section).

Kang et al. teaches that selenium is useful as lowering cholesterol level in subject taking high fat diet (See the abstract).

Pondimin monograph teaches fenfluramine is useful in increasing glucose utilization (see pharmacology Section).

Keown et al. teaches sympathomimetic agents, such as yohimbine and phendimetrazine, as useful in increasing fat metabolism and lowering serum cholesterol level in the amount from about 0.001 to 99.90% (See particularly page 9, lines 8-16; also claim 5).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ all the herein claimed agents, in the herein claimed amount, into the method of treating the side effects of ketogenic diet.

One of ordinary skill in the art would have been motivated to employ all the herein claimed agents, in the herein claimed amount, into the method of treating the side effects of ketogenic diet. All the agents herein can help relieving one of the side effects of ketogenic diet: centella asiatica, which contains the triterpene, can be useful to treat fatigue since it is a mild stimulant; selenium is useful in treating hypercholesterolemia because it can lower the cholesterol level; fenfluramine is useful for hyperglycemia because it can increase the utilization of glucose and causing hypoglycemia; yohimbine and phendimetrazine are useful for hypercholesterolemia. One of ordinary skill in the art would know that side effects of ketogenic diets include hypercholesterolemia, hyperglycemia, hyperuricemia, fatigue, change in mental status, nausea, and vomiting. Therefore, combining and employing two or more agents which are known to be useful to treat side effects of ketogenic diet individually into a single method useful for the very same purpose is prima facie obvious. See *In re Kerkhoven*

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205 USPQ 1069. Furthermore, the optimization of result effect parameters (i.e., dosage range, dosing regimens) is obvious as being within the skill of the artisan.

It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, claims are drawn to synergistic activities; however, no showing in the instant specification to demonstrate such activities. There is no data from the examples disclosed in the instant specification for the evaluation of the unexpected results is present. Therefore, unexpected results are not seen to be present in the instant specification.

### ***Response to Arguments***

Applicant's arguments and declaration filed June 19, 2003 averring synergistic effects being recited in the claims have been fully considered but they are not persuasive. As discussed above, applicants have the burden to demonstrate synergistic effects; however, from the data in the instant specification, no such data is present. As for the data shown in the declaration filed June 19, 2003, the shown is not clear whether

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the hypocholesterolemia or hypoglycemic effects as more than additive or not because it is not clear the hypocholesterolemia or hypoglycemic effects of each of the agents individually.

Applicant's arguments filed June 19, 2003 averring metformin not significantly affecting HDL and triglyceride have been fully considered but they are not persuasive. As discussed above, the side effect of ketogenic diet includes hypercholesterolemia, not hypertriglyceridemia. Examiner notes that HDL is the so called "good cholesterol" which should not be lowered. Therefore, since metformin decreases LDL, but not HDL, it is useful in treating patient are in risk to have hypercholesterolemia, such as those who is having ketogenic diet.

Applicant's arguments filed June 19, 2003 averring ursodeoxycholic acid not significantly affecting triglyceride have been fully considered but they are not persuasive. As discussed above, the side effect of ketogenic diet includes hypercholesterolemia, not hypertriglyceridemia. Therefore, since ursodeoxycholic acid decreases LDL, it is useful in treating patient are in risk to have hypercholesterolemia, such as those who is having ketogenic diet.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui  
Patent Examiner

  
SREENI PADMANABHAN  
PRIMARY EXAMINER

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